UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,374	02/24/2004	Marshall L. Summar	1242/58	1629

25297 7590 07/25/2008

JENKINS, WILSON, TAYLOR & HUNT, P. A.
Suite 1200 UNIVERSITY TOWER
3100 TOWER BLVD.,
DURHAM, NC 27707

EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
07/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/785,374	SUMMAR ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,18-23,25-29 and 34-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,18-23,25-29 and 34-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0208*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is responsive to the Response including a complying complete set of claims filed May 2, 2008. Claims 1, 5-6, 18, and 25 have been amended, claims 11-17, 24, and 30-33 have been canceled, and claims 35-38 have been added. Claims 1-10, 18-23, 25-29, and 34-38 are now pending and under consideration. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and/or objections not reiterated in this action have been withdrawn. This action includes a new obviousness-type double patenting rejection over divisional application 12/122,117, filed May 16, 2008, and is therefore **NON-FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

3. It is noted that applicant's amendments and arguments with respect to claim 25 (and claims dependent therefrom) are persuasive. The claim as amended finds support in the '823 patent, and is therefore entitled to an effective filing date of June 1, 2000.

Claim Rejections - 35 USC § 112

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS:

4. Claims 18-23 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18-23 and 37 are indefinite because it is not clear whether the method of the claims must be performed on a subject "suffering from sub-optimal urea cycle function" (as stated in the preambles of claim 18 and 37) or whether the method may be performed on any "subject in need thereof" (as indicated in the "administering" step of the claim). The relationship between the two referenced subjects is not made clear by the language of the claims, and applicant's claim language does not clearly apprise one of skill in the art as to what types of subjects are embraced by the claims, as is necessary to avoid infringement. Accordingly, clarification is required.

Claim Rejections - 35 USC § 102

5. Claims 1-4, 6-10, 18-23, 25-29, and 36-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Waugh (US 5,874,471A [23 February 1999]). **It is noted that applicants' amendments necessitated the new grounds of rejection included herein (including the inclusion of new claims 36-38 in the rejection).**

Waugh discloses methods in which citrulline is administered to a subject to achieve various therapeutic and/or prophylactic effects (see entire reference). It is noted that Waugh teaches that their methods function by increasing the availability of substrate for nitric oxide production (see, e.g., col 10, line 61-col 11, line 17).

Waugh discloses the administration of citrulline to humans "in dosage range from about 1.7 to about 20 grams per day" to achieve "beneficial therapeutic effects" for a variety of conditions (see col 11, lines 18-27). Waugh further discloses the oral administration of capsules containing approximately 876 mg of citrulline (see, e.g., col 17, lines 1-6). Thus, Waugh discloses administration of a dose of citrulline meeting the

requirements of, e.g., dependent claims 8-9, 21-22, and 28-29, and within the range disclosed in the specification at page 51. With regard to the amendment of independent claims 1, 18, and 25 to reference a subject "under conditions of sub-optimal urea cycle function" or suffering from sub-optimal urea cycle function" (and with regard to such limitations in new claims 36-38), it is noted that Waugh teaches that his methods are contemplated "both in normal, healthy persons and in individuals with reduced catalytic activities of these enzymes in disease states" (col 13, lines 6-8).

With further regard to dependent claim 3, it is noted that the language of the claim does not result in any manipulative difference between the claimed invention and the method of Waugh; as Waugh disclose administration of citrulline in a manner meeting the requirements of the claim, Waugh also inherently anticipates the methods of claim 3. Regarding the inventions of claims 4 and 6, it is noted that Waugh's teaching of the prevention of "angiostenosis after angioplasty" (see col 11, lines 18-27) constitutes a type of "cardiac surgery" meeting the requirements of claim 6. With regard to claim 18 and claims dependent therefrom, which recite the elected species of "pulmonary hypertension," the claims as written merely require the administration of citrulline in a "therapeutically effective" amount, and (as discussed above) Waugh clearly teaches the administration of citrulline in dosages encompassed by the claims, and administration to subjects with "reduced catalytic activities" of urea cycle enzymes in association with disease states, such that Waugh inherently anticipates the claimed invention. There is no manipulative difference between the method of Waugh and that

of the claims. With further regard to the preamble of claim 18, reciting "treating or preventing….pulmonary hypertension," it is also noted that MPEP 2111.02 states:

> If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir.1999).

In the instant case, the preamble of the claim merely recites the intended use of the invention, and Waugh's disclosure of a method step meeting the requirements of the claim anticipates the claimed invention.

With further regard to claim 25 and claims dependent therefrom, it is again noted that Waugh discloses that his method functions by increasing the availability of substrate for nitric oxide production (see, e.g., col 10, line 61-col 11, line 17); thus, the method disclosed by Waugh also achieves the objective of "raising a level of a nitric oxide precursor."

The reply traverses the rejection on the following grounds.

The reply argues that the claims as amended require subjects suffering from suboptimal urea cycle function (and associated disorders). The reply urges that Waugh teaches citrulline supplementation for "better health and amelioration of diseases that are not urea-cycle enzyme/substrate liver disorders," citing col 10, lines 41-45. Applicants argue that Waugh teaches away from the claimed invention, apparently interpreting the term "urea-cycle enzyme/substrate liver disorders" as being equivalent to "sub-optimal urea cycle function." The reply also argues that Waugh teaches methods in which excessive doses of citrulline are administered for purposes of "over-

supplementation," in contrast to the methods of the claims, which are drawn to the treatment of disorders. These arguments have been thoroughly considered but are not persuasive. While the examiner concurs that Waugh excludes "liver disorders" per se, Waugh's teachings clearly encompass treatment of other diseases/conditions associated with reduced catalytic activity, and specifically teach the treatment of conditions encompassed by applicant's claims, as indicated above. Further, the species elected by applicants were not, e.g., hepatitis or cirrhosis (as recited in, e.g., dependent claim 5), but cardiac surgery and pulmonary hypertension. Further, it is again noted that Waugh clearly does teach citrulline supplementation for disease/disorder treatment (as cited above), and that applicant's claims encompass the use of the same dosages taught by Waugh. Accordingly, applicant's arguments are not persuasive.

Claim Rejections - 35 USC § 103

6. Claims 5 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waugh (US 5,874,471A [23 February 1999]) in view of Kaesemeyer (US 5,767,160A [16 June 1998]). **It is noted that applicants' amendments necessitated the new grounds of rejection included herein (including the inclusion of new claim 35 in the rejection).**

Waugh discloses methods in which citrulline is administered to a subject to achieve various therapeutic and/or prophylactic effects (see entire reference). It is noted that Waugh teaches that their methods function by increasing the availability of substrate for nitric oxide production (see, e.g., col 10, line 61-col 11, line 17).

Waugh discloses the administration of citrulline to humans “in dosage range from about 1.7 to about 20 grams per day” to achieve “beneficial therapeutic effects” for a variety of conditions (see col 11, lines 18-27). Waugh further discloses the oral administration of capsules containing approximately 876 mg of citrulline (see, e.g., col 17, lines 1-6). Thus, Waugh discloses administration of a dose of citrulline within the ranges disclosed in the specification at page 51. With regard to the amendment of independent claim 1 (from which claims 5 and 34 depend) to reference a subject “under conditions of sub-optimal urea cycle function,” it is noted that Waugh teaches that his methods are contemplated "both in normal, healthy persons and in individuals with reduced catalytic activities of these enzymes in disease states" (col 13, lines 6-8).

While Waugh discloses the administration of citrulline for “vasoprotection” (see, e.g., col 12, lines 20-31) and in the prevention or treatment of “vasospastic diseases,” preeclampsia and the “prevention of angiostenosis after angioplasty” (see, e.g., col 11, lines 18-27), Waugh does not disclose the administration of citrulline therapy to a subject suffering from pulmonary hypertension (as set forth in claim 5 and 35) or a subject exposed to or about to be exposed to the environmental stimulus of “increased postoperative pulmonary vascular tone associated with cardiac surgery” (as set forth in claim 34).

Kaesemeyer teaches the use of arginine and its “biological equivalent” citrulline in the treatment of pulmonary hypertension as well as “perioperative hypertension” and “control of blood pressure in the treatment of hypertensive crisis,” as well as in the

treatment and prevention of various complications of heart surgery (see entire reference, particularly col 4 lines 36-60 and col 6, lines 5-45).

In view of the teachings of Kaesemeyer, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered citrulline in the manner disclosed by Waugh to a subject suffering from pulmonary hypertension or to a subject exposed to or about to be exposed to the environmental stimulus of "increased postoperative pulmonary vascular tone associated with cardiac surgery." As Kaesemeyer suggests the use of citrulline in the treatment of pulmonary hypertension as well as in a wide variety of other types of hypertension and for the treatment of cardiac surgery complications, an ordinary artisan would have been motivated to have administered citrulline as described by Waugh to subjects suffering from these conditions for the advantage of alleviating hypertension and reducing pulmonary vascular tone following cardiac surgery, as suggested by the teachings of Kaesemeyer.

The response traverses the rejection on the grounds that the Waugh reference is deficient as a primary references for the same reasons noted above in section 5, and on the grounds that the Kaesemeyer does not cure the deficiencies of Waugh with regard to a teaching or suggestion for treating subjects suffering from sub-optimal urea cycle function. Applicant's arguments with regard to the Waugh reference are addressed above in section 5, and the response to those arguments applies equally herein. Further, Kaesemeyer was not cited for a teaching of subjects suffering from sub-optimal urea cycle function, but for its teachings with respect to treatment of

pulmonary hypertension with citrulline, as indicated above. Accordingly, applicant's arguments are not persuasive.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-4, 7-10, 18-23, 25-29, and 37-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 8-14, and 17-21 of copending Application No. 12/122,117 (filed May 16, 2008). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The claims of the '117 application recite steps of administering citrulline in dosages encompassed by the instant claims to subjects exhibiting "suboptimal urea cycle function" comprising "decreased urea cycle intermediate production" (see text of

claims 3-4, 1—14). The instant claims differ from the '117 claims in that the instant claims are drawn to treating different effects or conditions resulting from suboptimal urea cycle function (e.g., decreased nitric oxide formation in the instant claims as compared to hyperammonemia in the '117 claims). However, the actual steps and types of subjects employed in the methods of each of the applications are the same, such that the '117 claims anticipate the instant claims. With particular regard to instant claim 18 and claims dependent therefrom, it is noted that the method is practiced on a subject "suffering from sub-optimal urea cycle function" (as opposed to, e.g., a subject actually suffering from pulmonary hypertension). Thus, the instant claims and the ''117 claims are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Terminal Disclaimer

9. The terminal disclaimer filed on January 14, 2008 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent 6,743,823 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday through Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634

Diana B. Johannsen
Primary Examiner
Art Unit 1634